b.) Remarks

Claims 37 and 43 have been amended in order to correct grammatical errors. No new matter has been added.

Claims 37 and 43-44 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is addressed by the foregoing amendment.

Claims 37 and 43-44 are rejected under 35 U.S.C. §103(a) as being obvious over Thiele (U.S. Patent No. 5,939,535) taken with Karmali (U.S. Patent No. 6,184,227), Yamahara (*Nature Medicines*, 1995) and/or JP 10046142.

According to the Examiner, Thiele discloses alcohol increases levels of lipid peroxidation, acetaldehyde and malondialdehyde causing liver injury. Malondialdehyde is formed by peroxidation of polyunsaturated fatty acids and oxidative degradation of deoxyribose by free radical hydroxy. Karmali is cited as teaching administering antioxidants to inhibit oxidation of ethanol and acetaldehyde toxicity, and Yamahara teaches that *Hydrageae Dulcis Folium* ethanol extract exhibits radical and lipid oxidation inhibition. JP 10046142 teaches that *Saxifrage stolonifera* exhibit better antioxidant properties than conventional antioxidants.

This rejection is respectfully traversed.

In the Office Action, the Examiner states that

> Karmali discloses that the administration of antioxidants inhibits the oxidation of ethanol and the toxic effects of acetaldehyde (col. 3, line 45, through col. 4, line 22).

Respectfully submitted, this is incorrect.

Rather, in Karmali, the effective essential component to inhibit the oxidation of ethanol and the toxic effects of acetaldehyde is aminoimidazole carboxamide (AICA) and not antioxidants (see column 3, line 33 to column 4, line 28, especially col. 3, lines 45-49).

Although the Examiner relies on the objects discussed at column 4, lines 3-10, ("treatment of liver damage caused by alcohol which comprises administering a salt of AICA and an antioxidant selected from the group of...") a closer reading of Karmali reveals that it teaches AICA is the effective component and antioxidants such as vitamin E, vitamin C, vitamin A are optional. See col. 1, lines 17-25 and 34-46 of Karmali wherein

> The present invention is directed to methods and compositions for the prevention and/or inhibition of tissue injury caused by alcohol, therapeutically useful drugs as well as by industrial, dietary and environmental toxins, by administration of salts of aminoimidazole carboxyamide (AICA). Use of the entire group of organic acid salts and inorganic acid salts of 5-aminoimidazole carboxamide rather than only those obtained from orotic acid are encompassed by the methods of the invention.
>
> * * * * * * *

> The methods involve administering to an individual consuming alcohol, therapeutic drugs and/or exposed to xenobiotic agents, an effective dose of aminoimidazole carboxamide with or without antioxidants, including, but not limited to vitamin E, vitamin C, vitamin A and its derivatives, glutathione, N-acetylcysteine or magnesium gluconate. In the practice of the invention, compositions containing salts of AICA are used to detoxify harmful and noxious agents or toxins, to inhibit bioactivation of agents to harmful electrophiles or free radicals, to inhibit suppression of cell-mediated or humoral immune mechanisms, to stimulate the regeneration of target cells of the damaged tissue and to inhibit the failure of energy supply.

That is to say, contrary to the Examiner's assertion, Karmali does not teach that any antioxidants, such as vitamin E, C or A, itself has an effect of inhibiting the oxidation of ethanol and the toxic effects of acetaldehyde.

Moreover, Yamahara does not teach that the methanol extract of Hydrangea Dulcis Folium contains AICA.[1] Therefore, for at least one the above reasons, the Office Action has not made out a prima facie case of obviousness.

In any event, the Examiner further states that

> Yamahara et al. disclose that the methanol extract of Hydrangea Dulcis Folium exhibits radical inhibiting effect and inhibitory effect on oxidation of lipids (page 2, lines 7-9 and Experiment on pages 2-6 of the English translation).

Respectfully submitted, this is also without basis in fact. Those of ordinary skill are well-aware that the correlation between the inhibitory activity on lipid peroxidation *in vitro* and the protective potency against liver injury *in vivo* is very low.

[1] Nor does Yamahara teach, for that matter, methanol extracts of Hydrangea Dulcis Folium contain an antioxidant such as vitamin E, C or A.

Those of ordinary skill are also well-aware that liver injuries such as hepatonecrosis cannot be protected only by inhibiting lipid peroxidation, as evidenced by Suzuki, Yakugaku Zasshi Vol. 110, No. 9 (1990) 697-701, the English translation of which was submitted with Applicants' June 16, 2006 Amendment.

Therefore, even if, *arguendo*, Yamahara did teach that methanol extracts of Hydrangea Dulcis Folium exhibit radical inhibiting effect and inhibitory effect on oxidation of lipids, it would still have been unobvious for one of ordinary skill in the art to use such extracts to protect the liver function from alcohol intake in view of the teachings of Thiele and Karmali.

As to JP 10046142, that reference discloses that extracts of Saxifrage stolonifera exhibit better antioxidant properties than conventional antioxidants. However, the pending claims do not recite Saxifrage Stolonifera.

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns are now overcome and the claims are now in allowable condition. Accordingly, reconsideration and allowance of this application is earnestly solicited.

Claims 37, 43 and 44 remain presented for continued prosecution.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

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